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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

ACTELION PHARMACEUTICALS LTD. and ACTELION PHARMACEUTICALS US, INC. Plaintiffs, v. BRISTOL-MYERS SQUIBB CO., CELGENE CORP., and CELGENE INTERNATIONAL II SARL, Defendants.	C. A. No. _____ **COMPLAINT FOR PATENT INFRINGEMENT** **JURY TRIAL DEMANDED**

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiffs Actelion Pharmaceuticals Ltd. and Actelion Pharmaceuticals US, Inc. (collectively, "Actelion"), for their Complaint against Celgene Corporation, Bristol-Myers Squibb Company, and Celgene International II Sarl (collectively, "Defendants"), allege as follows:

INTRODUCTION

1. A class of drugs called *selective $S1P_1$ receptor agonists* interact with $S1P_1$ receptors in the lymph nodes, and reduce the numbers of lymphocytes (white blood cells) in circulation. Such reduced lymphocyte levels may be useful in treating certain autoimmune and inflammatory diseases. Drugs in this class have been approved for treatment of relapsing multiple sclerosis ("RMS") and ulcerative colitis ("UC"). This case—a competitor case, not a Hatch-Waxman case—is about the way

these selective $S1P_1$ receptor agonists are administered.

2. Actelion markets PONVORY® (ponesimod), a selective $S1P_1$ receptor agonist for the treatment of RMS in adults. The FDA approved PONVORY® in March 2021.

3. During its development work, Actelion made a surprising discovery. Namely, selective $S1P_1$ receptor agonist drugs, although useful to treat RMS and other illnesses such as UC, can have a potentially major side effect in humans: these drugs can dramatically suppress a patient's heart rate. Thus, taking selective $S1P_1$ receptor agonist drugs can cause a dangerous condition called bradycardia (a sharp drop in heart rate).

4. To address this problem, Actelion invented and patented a new way of administering selective $S1P_1$ receptor agonists to treat RMS and other diseases. Specifically, Actelion discovered that a particular dosing regimen could desensitize the heart to acute heart rate drops, while still providing patients with the benefits of selective $S1P_1$ receptor agonist drugs to treat RMS and other diseases.

5. On April 9, 2019, the United States Patent and Trademark Office ("USPTO") issued U.S. Patent No. 10,251,867 (the "'867 patent") claiming Actelion's invention: a method of administering a selective $S1P_1$ receptor agonist drug involving an "initial treatment phase" followed by a "dose up-titration."

6. Defendants Bristol-Myers Squibb Company, Celgene Corporation, and Celgene International II Sarl (collectively, "Defendants") make and sell ZEPOSIA®, which is a selective $S1P_1$ receptor agonist drug to treat RMS and UC. The FDA approved ZEPOSIA® in March 2020 for the treatment of adults with RMS and in May 2021 to treat adults with moderately to severely active UC.

7. ZEPOSIA®'s instructions for use in its approved labeling, as well as its "7-DAY STARTER PACK" blister package for the first week's capsules, both explicitly instruct doctors and patients to administer the drug using a dosing regimen that "attenuates the magnitude of heart rate

reductions"—and which infringes the '867 patent. Defendants are aware of the '867 patent and are making tens of millions of dollars selling ZEPOSIA® together with instructions on how to use it to infringe the '867 patent. Defendants are profiting from Actelion's research by leveraging Actelion's patented dosing regimen invention to sell Defendants' own selective $S1P_1$ receptor agonist drug.

8. Actelion brings this suit seeking damages for past infringement and to prevent Defendants from infringing the '867 patent.

NATURE OF THE ACTION

9. This is a civil action for infringement of United States Patent No. 10,251,867. This action is based upon the Patent Laws of the United States, 35 U.S.C. § 100 *et seq*.

PARTIES

10. Plaintiff Actelion Pharmaceuticals Ltd. is a limited company organized and existing under the laws of Switzerland, having a principal place of business at Gewerbestrasse 16, CH-4123, Allschwil, Switzerland.

11. Plaintiff Actelion Pharmaceuticals US, Inc. is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 1125 Trenton-Harbourton Road, 1st Floor/B-Wing, Titusville, New Jersey, 08560.

12. Actelion Pharmaceuticals Ltd. and Actelion Pharmaceuticals US, Inc. are pharmaceutical companies dedicated to advancing the treatment of complex diseases. Each are indirect, wholly-owned subsidiaries of Johnson & Johnson.

13. On information and belief, Defendant Bristol-Myers Squibb Company ("BMS") is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at Route 206 and Province Line Road, Princeton, New Jersey 08540. On information and belief, BMS is in the business of manufacturing, distributing, and selling pharmaceutical products throughout the United States, either on its own or through its affiliates, and BMS is headquartered in,

and regularly conducts business in, New Jersey. On information and belief, BMS is the corporate parent of Celgene Corporation.

14. On information and belief, Defendant Celgene Corporation ("Celgene Corp.") is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 86 Morris Avenue, Summit, New Jersey 07901. On information and belief, Celgene Corp. is a wholly-owned subsidiary of BMS. On information and belief, Celgene Corp. is in the business of manufacturing, distributing, and selling pharmaceutical products throughout the United States, either on its own or through its affiliates, and Celgene Corp. is headquartered in, and regularly conducts business in, New Jersey.

15. On information and belief, Defendant Celgene International II Sarl ("Celgene International") is a limited liability company organized and existing under the laws of Switzerland, having a principal place of business at Rue du Pre-Jorat 14, 2108 Couvet, Switzerland. On information and belief, Celgene International is a wholly-owned subsidiary of Celgene Corp. On information and belief, BMS is the ultimate corporate parent of Celgene International. On information and belief, Celgene International is in the business of manufacturing, distributing, and selling pharmaceutical products throughout the United States, either on its own or through its affiliates, and Celgene International regularly conducts business in New Jersey.

JURISDICTION AND VENUE

16. This is a civil action for patent infringement arising under the patent laws of the United States, 35 U.S.C. § 100 *et. seq.*, and in particular 35 U.S.C. § 271.

17. Subject matter jurisdiction is proper under 28 U.S.C. §§ 1331 and 1338(a).

18. This Court has personal jurisdiction over BMS because BMS maintains a principal place of business at Route 206 and Province Line Road, Princeton, New Jersey 08540. *See, e.g., Bristol-Myers Squibb Co. v. Lupin Ltd.*, No. 3:20-cv-07810-MAS-TJB, Dkt. 1 at ¶ 2 (D.N.J. June 25, 2020).

Additionally, BMS maintains multiple facilities within the state of New Jersey, including, for example, a 1.67 million square foot, 280-acre "New Jersey Corporate HQ." *See, e.g.,* https://www.bms.com/about-us/our-company/worldwide-facilities.html. On information and belief, BMS maintains continuous and systematic contacts with the state of New Jersey.

19. Additionally, on information and belief, BMS is in the business of manufacturing, distributing, and/or selling pharmaceutical products, including ZEPOSIA®, within the state of New Jersey. For example, on information and belief, BMS is a registered wholesaler with the New Jersey Department of Health, holding Registration No. 5000004. By way of further example, BMS's logo appears on the ZEPOSIA® label, stating that ZEPOSIA® is manufactured for BMS's subsidiary, "Celgene Corporation, Summit, New Jersey." On information and belief, BMS has recruited and is recruiting personnel to market, distribute, and/or sell ZEPOSIA® throughout the United States, including in the state of New Jersey. As described further below, BMS has infringed and/or caused infringement of the '867 patent within this District.

20. Moreover, on information and belief, BMS has consented to the jurisdiction of this Court in several previous cases. *See, e.g., Merck Sharp & Dohme Corp. v. Bristol-Myers Squibb Co.*, No. 2:16-cv-02122-CCC-JBC (D.N.J.). BMS has itself filed complaints in this District, many of them involving assertion of patent rights. *See, e.g., Bristol-Myers Squibb Co. v. Lupin Ltd.*, No. 3:20-cv-07810-MAS-TJB (D.N.J. June 25, 2020); *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, No. 3:20-cv-03229 (D.N.J. Mar. 25, 2020); *Bristol-Myers Squibb Co. v. Dr. Reddy's Labs., Ltd.,* No. 1:12-cv-07800-NLH-KMW (D.N.J. Dec. 12, 2012); *Bristol-Myers Squibb Co. v. Apotex, Inc.*, No. 3:10-cv-05810-MLC-LHG (D.N.J. Nov. 8, 2010).

21. This Court has personal jurisdiction over Celgene Corp. because Celgene Corp. maintains its principal place of business at 86 Morris Avenue, Summit, New Jersey 07901. On information and belief, Celgene Corp. maintains continuous and systematic contacts with the State of

New Jersey.

22. Additionally, on information and belief, Celgene Corp. is in the business of manufacturing, distributing, and/or selling pharmaceutical products, including ZEPOSIA®, within the state of New Jersey. For example, on information and belief, Celgene Corp. is a registered manufacturer and wholesaler with the New Jersey Department of Health, holding Registration No. 5003533. By way of further example, the ZEPOSIA® label states that ZEPOSIA® is "[m]anufactured for: Celgene Corporation, Summit, NJ." As described further below, Celgene Corp. has infringed and/or caused infringement of the '867 patent within this District.

23. Moreover, on information and belief, Celgene Corp. has consented to the jurisdiction of this Court in several previous cases. *See, e.g.*, *Humana Inc. v. Celgene Corp.*, No. 2:19-cv-07532-ES-MAH (D.N.J.); *Jacobson v. Celgene Corp.*, No. 2:09-cv-04329-FSH-PS (D.N.J.); *Schwab Capital Trust v. Celgene Corp.*, No. 2:20-cv-03754-JMV-JBC (D.N.J.). Celgene Corp. has itself filed cases in this District, many of them involving the assertion of patent rights. *See, e.g.*, *Celgene Corp. v. Dr. Reddy's Labs., Ltd.*, No. 2:21-cv-02111-ES-MAH (D.N.J. Feb. 8, 2021); *Celgene Corp. v. Hetero Labs Ltd.*, No. 2:17-cv-03387-ES-MAH (D.N.J. May 11, 2017).

24. This Court has personal jurisdiction over Celgene International. On information and belief, Celgene International is in the business of manufacturing, distributing, and/or selling pharmaceutical products, including ZEPOSIA®, within the state of New Jersey. Additionally, Celgene International is listed as the applicant for New Drug Application ("NDA") No. 209899 for ZEPOSIA®. On information and belief, Celgene International has directly or indirectly infringed and/or caused infringement of the '867 patent within this District. In the alternative, as a foreign corporation, this Court has personal jurisdiction over Celgene International under Federal Rule of Civil Procedure 4(k)(2) because: (a) Actelion's claims arise under federal law; (b) Celgene International would be a foreign defendant not subject to personal jurisdiction in the courts of any State; and (c) Celgene

International has sufficient contacts with the United States as a whole including, but not limited to, on information and belief, filing the ZEPOSIA® NDA, manufacturing, distributing, and/or selling pharmaceutical products, including ZEPOSIA®, throughout the United States, and conducting systematic, routine, and continuous business with Celgene Corporation and BMS such that this Court's exercise of jurisdiction over Celgene International satisfies due process, and is consistent with the United States Constitution and Laws.

25. Venue is proper in this District pursuant to 28 U.S.C. § 1391 and 28 U.S.C. § 1400(b). Within this District, BMS and Celgene Corp. each carry out, aid and abet, contribute to, induce, and/or participate in the commission of acts of infringement with respect to their ongoing manufacture, distribution, and/or sale of ZEPOSIA®. Moreover, BMS and Celgene Corp. direct patients to administer and/or use, and healthcare providers to prescribe and/or administer, ZEPOSIA® in a manner that constitutes infringement within this District. BMS and Celgene Corp. maintain regular and established places of business within this District. For example, on information and belief, BMS maintains its corporate headquarters, and multiple other facilities, within this District through which BMS infringes, has committed or aided, abetted, contributed to, induced, and/or participated in the commission of, acts of infringement of the asserted patent that will lead to foreseeable harm and injury to Actelion. By way of further example, Celgene Corp. maintains its corporate headquarters, and multiple other facilities, within this District through which Celgene Corp. infringes, has committed or aided, abetted, contributed to, induced, and/or participated in the commission of, acts of infringement of the asserted patent that will lead to foreseeable harm and injury to Actelion.

26. Venue is proper in this District with respect to Celgene International under 28 U.S.C. § 1391(c) because, *inter alia*, Celgene International is a foreign entity, and is thus subject to suit in any jurisdiction in the United States, including the District of New Jersey.

BACKGROUND

Relapsing Multiple Sclerosis (RMS)

27. Multiple sclerosis ("MS") is an autoimmune disease that damages the central nervous system, including the brain and spinal cord. MS can affect people of all ages, though the typical age of onset is between 20 and 30. As of today, there is no cure.

28. In patients suffering from MS, the immune system attacks the insulating covers surrounding nerve cells. When these covers—called myelin sheaths—degrade, patients suffer debilitating nerve damage, along with symptoms such as pain, numbness, tingling, difficulty seeing, weakness, fatigue, trouble with balance, and lack of coordination.

29. One type of MS is called relapsing multiple sclerosis (again, "RMS"). Patients with RMS experience isolated attacks or flare-ups of the disease. During RMS attacks, the body accumulates lymphocytes—white blood cells that are part of the body's immune response—that gather around the inflamed nerve cell tissue. These lymphocytes attack the myelin sheaths, causing damage and scarring (sclerosis) that degrades nerve function. One way to treat RMS is by administering selective $S1P_1$ receptor agonist drugs, which may limit the number of lymphocytes available to attack nerve tissue.

Ulcerative Colitis (UC)

30. Another illness involving inflammation tied to lymphocyte action is ulcerative colitis (again, "UC"), an autoimmune and inflammatory disease that causes inflammation in the large intestine. UC can occur at any age, with typical diagnosis occurring between ages 30 and 40. As of today, there is no cure for UC.

31. In patients suffering from UC, an abnormal immune system response causes chronic inflammation in the lining of the large intestine. The inflammation causes sores or ulcers to form and patients suffer symptoms such as loose and urgent bowel movements, diarrhea, bloody stool, and

abdominal pain, along with symptoms away from the intestine such as loss of appetite, weight loss, nausea, fever, fatigue, and anemia. Some patients experience debilitating pain and life-threatening complications.

32. Lymphocytes, which migrate from the lymphatic system to peripheral circulation that reaches the intestines, contribute to UC inflammation. One way to treat UC is by administering selective $S1P_1$ receptor agonist drugs, which may reduce the number of lymphocytes in peripheral circulation.

$S1P_1$ Receptor Agonists and Their Safe Administration

33. The lymphocytes that degrade nerve sheaths in MS and contribute to inflammation in UC are controlled in part by a biological circuit—biochemical switches called S1P receptors. (S1P stands for sphingosine-1-phosphate, a lipid that acts in the body as a signaling molecule.) Lymphocyte levels in the blood can be decreased if S1P receptors are activated with an agonist (which is a chemical that binds to and activates a biological receptor), and therefore S1P receptor agonists have therapeutic potential in a variety of diseases.

34. There are five sub-types of S1P receptors in the body, which researchers have characterized and numbered ($S1P_1$ through $S1P_5$). Defendants' ZEPOSIA® is a compound which selectively activates one of those five receptor sub-types, namely the "$S1P_1$" receptor. As such, it is a selective $S1P_1$ receptor agonist—which is the class of drug covered in the '867 patent method.

35. Actelion discovered, in addition to desired therapeutic effects, selective $S1P_1$ receptor agonists can transiently and dramatically reduce heart rate in humans. Thus, administering an $S1P_1$ receptor agonist to a patient can cause a dangerous condition known as bradycardia (a sharp drop in heart rate) and related side effects. Actelion discovered that the effects wane with repeated dosing and certain dosage amounts, making when and how a patient is first administered an $S1P_1$ receptor agonist critical for safety. Accordingly, Actelion invented the method disclosed and claimed in the '867 patent

to permit patients to begin administration of an $S1P_1$ receptor agonist safely.

The '867 Patent

36. The '867 patent is titled "Dosing Regimen for a Selective $S1P_1$ Receptor Agonist," and was duly and legally issued by the USPTO on April 9, 2019. A true and correct copy of the '867 patent is attached hereto as Exhibit A.

37. Actelion Pharmaceuticals Ltd. owns the '867 patent. Actelion Pharmaceuticals US, Inc. holds an exclusive license to sell under the '867 patent, including the right to enforce the '867 patent.

38. The '867 patent discloses and claims a novel method for administering a selective $S1P_1$ receptor agonist to desensitize the heart to acute heart rate reduction, the method for administering which includes an initial treatment phase followed by dose up-titration to the target dose to safely achieve the therapeutic effects of the selective $S1P_1$ receptor agonist.

DEFENDANTS' INFRINGEMENT OF THE '867 PATENT

39. Defendants engage in the commercial manufacture, use, offer for sale, sale, and/or importation of ZEPOSIA® in the United States. ZEPOSIA® contains ozanimod, a selective $S1P_1$ receptor agonist, that is indicated for the treatment of relapsing forms of MS (i.e., RMS) and moderately to severely active UC in adults.

40. On information and belief, Defendants manufacture, use, offer for sale, sell, and/or import ZEPOSIA® with the label approved by the FDA in the United States. A true and correct copy of the ZEPOSIA® label is attached hereto as Exhibit B.

41. On information and belief, patients and healthcare providers in the United States and within this District have used and continue to use ZEPOSIA® in accordance with the label provided and authored by Defendants.

42. On information and belief, BMS, both individually and in concert with Celgene Corp. and Celgene International, makes, uses, offers to sell, sells, and/or imports ZEPOSIA® in the United

States. On information and belief, BMS, both individually and in concert with Celgene Corp. and Celgene International, markets and distributes ZEPOSIA® within the United States, including in this District. On information and belief, BMS, both individually and in concert with Celgene Corp. and Celgene International, authored at least portions of the label approved by the FDA for ZEPOSIA®, which instructs its customers how to use ZEPOSIA® for its approved indications.

43. On information and belief, BMS maintains the websites located at www.zeposia.com and www.zeposiahcp.com, which include links to the ZEPOSIA® label. On information and belief, BMS has published and/or distributed press releases and advertisements related to its commercial launch and marketing of ZEPOSIA® in the United States. For example, BMS published and distributed a press release titled "Bristol Myers Squibb Announces Commercial Launch and Availability of ZEPOSIA® (ozanimod), a New Oral Treatment for Relapsing Forms of Multiple Sclerosis" on June 1, 2020, a true and correct copy of which is attached hereto as Exhibit C. On information and belief, BMS maintains www.zeposia.com and www.zeposiahcp.com and has published and/or distributed press releases and advertisements for the purpose and intent of marketing ZEPOSIA® to its customers in the United States, including in this District.

44. On information and belief, Celgene Corp., both individually and in concert with BMS and Celgene International, makes, uses, offers to sell, sells, and/or imports ZEPOSIA® in the United States. On information and belief, Celgene Corp., both individually and in concert with BMS and Celgene International, markets and distributes ZEPOSIA® within the United States, including in this District. On information and belief, Celgene Corp., both individually and in concert with BMS and Celgene International, authored at least portions of the label approved by the FDA for ZEPOSIA®, which instructs customers how to use ZEPOSIA® for its approved indication.

45. On information and belief, Celgene Corp., both individually and in concert with BMS and Celgene International, manufactures or causes to be manufactured on its behalf ZEPOSIA® for

use, offer for sale, sale, and/or importation in the United States. On information and belief, Celgene Corp., both individually and in concert with BMS and Celgene International, manufactures or causes to be manufactured on its behalf ZEPOSIA®, with the intent that ZEPOSIA® is distributed to its customers in the United States, including in this District, with the FDA-approved ZEPOSIA® label.

46. On information and belief, Celgene International, both individually and in concert with BMS and Celgene Corp., makes, uses, offers to sell, sells, and/or imports ZEPOSIA® in the United States. On information and belief, Celgene International, both individually and in concert with BMS and Celgene Corp., markets and distributes ZEPOSIA® within the United States, including in this District. On information and belief, Celgene International, both individually and in concert with BMS and Celgene Corp., authored at least portions of the label approved by the FDA for ZEPOSIA®, which instructs customers how to use ZEPOSIA® for its approved indication.

47. Celgene International is the listed applicant for NDA No. 209899 for ZEPOSIA®.

48. On information and belief, BMS, Celgene Corp, and Celgene International act as agents of one another and/or operate in concert as integrated parts of the same business group with respect to ZEPOSIA®.

Defendants' Knowledge, Intent, and Willful Infringement

49. On information and belief, Defendants have known of the '867 patent at least since the date that it issued. On information and belief, Defendants are sophisticated entities that are in the business of manufacturing, distributing, and selling pharmaceutical products (including ZEPOSIA®) in the United States. Accordingly, on information and belief, Defendants regularly survey and analyze the patent literature and have encountered the '867 patent.

50. On information and belief, Defendants analyzed whether they have freedom to operate and conducted such an analysis at least prior to commercial launch of ZEPOSIA®. On information and belief, Defendants knew of the '867 patent and their infringement thereof at least before ZEPOSIA®'s

commercial launch in the United States.

51. On information and belief, Defendants also had knowledge of the ’867 patent because Celgene Corp. is listed as the applicant and assignee on at least three patents that cite U.S. Patent No. 8,785,484 (“the ’484 patent”) on their face. The ’484 patent is a parent of the ’867 patent, claiming priority to PCT/IB2008/050995. Specifically, United States Patent Nos. 11,014,897, 11,013,723, and 11,014,940 each cite to the ’484 patent on their face. Accordingly, on information and belief, Celgene Corp. was aware of the ’484 patent and its family members (including the ’867 patent) no later than May 28, 2020, the date the ’484 patent was cited by applicant Celgene Corp. to the USPTO in each of the corresponding applications for United States Patent Nos. 11,014,897, 11,013,723, and 11,014,940. On information and belief, BMS, Celgene Corp., and Celgene International act as agents of one another and/or operate in concert as integrated parts of the same business group with respect to ZEPOSIA® and have communicated any knowledge of the ’867 patent to each other.

52. On information and belief, Defendants are also aware of their past and continued infringement given the similarity of ZEPOSIA® and its accompanying label to the examples disclosed in the ’867 patent.

53. Moreover, and at minimum, this Complaint provides Defendants notice of the ’867 patent and their infringement thereof.

54. Despite their knowledge of the ’867 patent and related infringement, Defendants continue to knowingly and willfully infringe the ’867 patent by making, using, offering to sell, selling, and/or importing ZEPOSIA® and instructing patients and healthcare providers to use ZEPOSIA® according to its FDA-approved label. On information and belief, Defendants have not made any changes to ZEPOSIA® or its label to avoid infringement of the ’867 patent. Defendants’ knowing and intentional infringement of the ’867 patent is egregious, willful, and in bad faith.

COUNT I
(Infringement of the '867 Patent by Defendants)

55. Actelion incorporates each of the preceding paragraphs 1 to 54 as if fully set forth herein.

56. The '867 patent was duly and legally issued by the United States Patent and Trademark Office on April 9, 2019. Actelion Pharmaceuticals Ltd. is the assignee and owner of the '867 patent and has the right to sue for infringement thereof. Actelion Pharmaceuticals US, Inc. holds an exclusive license to the '867 patent, including the right to enforce the '867 patent.

57. The ZEPOSIA® label directs patients to administer and/or use, and healthcare providers to prescribe and/or administer, ZEPOSIA® in a safe manner that meets each limitation of at least claims 1, 2, 4, 5, and 6 of the '867 patent.

'867 Patent Independent Claim 1

58. Such use meets each limitation of independent claim 1 of the '867 patent, which recites:

> 1. A method for administering a selective $S1P_1$ receptor agonist or a pharmaceutically acceptable salt thereof to a human subject in need thereof wherein during an initial treatment phase the selective $S1P_1$ receptor agonist or pharmaceutically acceptable salt thereof is administered at a dose which induces desensitization of the heart to acute heart rate reduction said dose being below the target dose, and at a dosing frequency that sustains desensitization of the heart, until no further acute heart rate reduction occurs, followed by dose up-titration to the target dose of the selective $S1P_1$ receptor agonist or pharmaceutically acceptable salt thereof.

59. The ZEPOSIA® prescribing information ("ZEPOSIA® label") provides instructions for a method to administer ZEPOSIA® which contains ozanimod, "supplied as ozanimod hydrochloride (HCl)." *See* Exhibit B at 11 (Description). As indicated on the ZEPOSIA® label, ZEPOSIA® "is a sphingosine 1-phosphate receptor modulator [(S1P receptor agonist)]."

---------- INDICATIONS AND USAGE ----------

ZEPOSIA is a sphingosine 1-phosphate receptor modulator indicated for the treatment of:

- Relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. (1)
- Moderately to severely active ulcerative colitis (UC) in adults. (1)

----------DOSAGE AND ADMINISTRATION----------

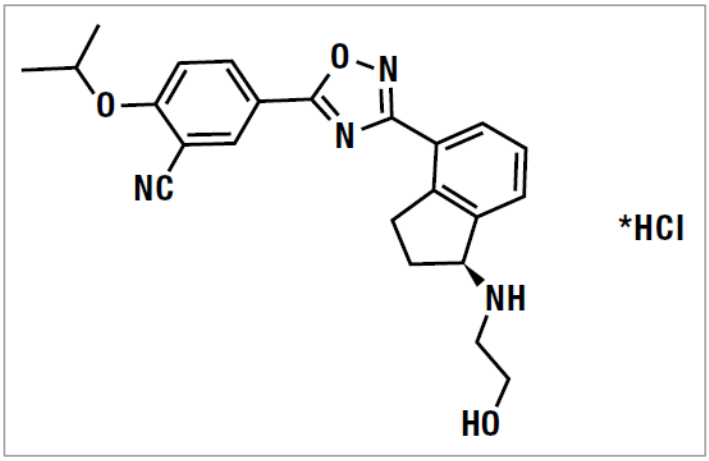
- Assessments are required prior to initiating ZEPOSIA. (2.1)
- Titration is required for treatment initiation. (2.2)
- The recommended maintenance dosage is 0.92 mg orally once daily. (2.2)
- If a dose is missed within the first 2 weeks of treatment, reinitiate with the titration regimen. If a dose is missed after the first 2 weeks of treatment, continue treatment as planned. (2.3)

---------- DOSAGE FORMS AND STRENGTHS ----------

Capsules: 0.23 mg, 0.46 mg, 0.92 mg ozanimod (3)

See Exhibit B at Indications and Usage.

60. The ZEPOSIA® label also states that "ZEPOSIA contains ozanimod, a sphingosine 1-phosphate receptor modulator [(S1P receptor agonist)] and is supplied as ozanimod hydrochloride (HCl)," which has a chemical name of "5-(3-{(1S)-1-[(2-hydroxyethyl)amino]-2,3-dihydro-1*H*-inden-4-yl}-1,2,4-oxadiazol-5-yl)-2-[(propan-2-yl)oxy]benzonitrile, monohydrochloride," and the following chemical structure:



See Exhibit B at 11 (Description). The ZEPOSIA® label further states that "ZEPOSIA capsules are provided as hard gelatin capsules for oral administration, containing 0.23, 0.46, or 0.92 mg of ozanimod (equivalent to 0.25, 0.5, and 1 mg ozanimod HCl, respectively)." *See* Exhibit B at 11 (Description).

61. Ozanimod, the active ingredient in ZEPOSIA®, is a selective $S1P_1$ receptor agonist as

recited by Claim 1. The ZEPOSIA® label states that "[o]zanimod is a sphingosine 1-phosphate (S1P) receptor modulator [(agonist)] that binds with high affinity to S1P receptors 1 and 5," that "[o]zanimod blocks the capacity of lymphocytes to egress from lymph nodes, reducing the number of lymphocytes in peripheral blood," and "[o]zanimod has minimal or no activity on $S1P_2$, $S1P_3$, and $S1P_4$ [receptors]." *See* Exhibit B at 12.1 (Mechanism of Action).

62. The ZEPOSIA® label further instructs that ZEPOSIA® (ozanimod) capsules are indicated for administration to adult humans for the treatment of: "Relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease" and "Moderately to severely active ulcerative colitis (UC)." *See* Exhibit B at Indications and Usage.

63. Moreover, the ZEPOSIA® label instructs that "[t]itration is required for treatment initiation" as described in section 2.2 of the label. *See* Exhibit B at Dosage and Administration. Section 2.2 provides dosing instructions for the treatment initiation phase as follows:

2.2 Recommended Dosage for Multiple Sclerosis and Ulcerative Colitis

Initiate ZEPOSIA with a 7-day titration, as shown in Table 1 *[see Warnings and Precautions (5.2)]*. After initial titration, the recommended dosage of ZEPOSIA is 0.92 mg taken orally once daily starting on Day 8.

Swallow ZEPOSIA capsules whole, with or without food *[see Clinical Pharmacology (12.3)]*.

Table 1: Dose Titration Regimen

Days 1-4	0.23 mg once daily
Days 5-7	0.46 mg once daily
Day 8 and thereafter	0.92 mg once daily

2.3 Reinitiation of ZEPOSIA after Treatment Interruption

If a dose of ZEPOSIA is missed during the first 2 weeks of treatment, reinitiate treatment using the titration regimen *[see Dosage and Administration (2.2)]*.

If a dose of ZEPOSIA is missed after the first 2 weeks of treatment, continue with the treatment as planned.

See Exhibit B at 2.2 (Recommended Dosage for Multiple Sclerosis and Ulcerative Colitis).

64. The ZEPOSIA® label instructs a method for administering ZEPOSIA® involving an initial treatment phase followed by dose up-titration, with days 1-4 at 0.23 mg once daily (i.e., one quarter of the target dose), days 5-7 at 0.46 mg once daily (i.e., one half of the target dose), and days 8 and thereafter at 0.92 mg once daily (i.e., the target dose). *See* Exhibit B at 2.2 (Recommended Dosage for Multiple Sclerosis and Ulcerative Colitis). The initial treatment phase followed by dose-up titration instructed by the ZEPOSIA® label is nearly identical to the method described in the '867 patent: "4 days with 10 mg once daily [i.e., one quarter of the target dose], followed by 4 days with 20 mg once daily [i.e., one half of the target dose], and [thereafter] 40 mg once daily [i.e., the target dose]." '867 patent at 7:8-45 & Table 1.

65. The ZEPOSIA® label instructs that "[a]n up-titration schedule of ZEPOSIA 0.23 mg followed by doses of 0.46 mg, and 0.92 mg attenuates the magnitude of heart rate reductions." *See* Exhibit B at 12.2 (Pharmacodynamics). The ZEPOSIA® label's "WARNINGS AND PRECAUTIONS" also caution that "[s]ince initiation of ZEPOSIA may result in transient decrease in heart rate and atrioventricular conduction delays, an up-titration scheme should be used to reach the maintenance dosage of ZEPOSIA" and further that "[i]nitiation of ZEPOSIA without titration may result in greater decreases in heart rate." *See* Exhibit B at 5.2 (Bradyarrhythmia and Atrioventricular Conduction Delays).

66. The ZEPOSIA® label also instructs that "[i]f a dose of ZEPOSIA is missed during the first 2 weeks of treatment," that is if the once daily dosing frequency is not kept during the "7-day titration" or the following week, to "reinitiate the treatment using the titration regimen." *See* Exhibit B at 2.3 (Reinitiation of ZEPOSIA after Treatment Interruption).

67. The ZEPOSIA® label also states that in multiple sclerosis or ulcerative colitis patients who were administered ZEPOSIA® the "mean lymphocyte counts decreased to approximately 45% of baseline at 3 months" corresponding to "approximate mean blood lymphocyte counts 0.8 x 10^9/L," and

that "low lymphocyte counts were maintained during treatment with ZEPOSIA." *See* Exhibit B at 12.2 (Pharmacodynamics).

68. The ZEPOSIA® label's "PATIENT COUNSELING INFORMATION" instructs healthcare providers to "[a]dvise the patient to read the FDA-approved patient labeling (Medication Guide)," "[a]dvise patients that initiation of ZEPOSIA treatment may result in a transient decrease in heart rate," "[i]nform patients that to reduce this effect, dose titration is required," and "[a]dvise patients that the dose titration is also required if a dose is missed for 1 day or more during the first 14 days of treatment." *See* Exhibit B at 17 (Patient Counseling Information).

69. The ZEPOSIA® label also includes a Medication Guide for patients that instructs patients to "Read this Medication Guide before you start taking ZEPOSIA." *See* Exhibit B at Medication Guide. The Medication Guide states "ZEPOSIA may cause serious side effects, including . . . Slow heart rate (also known as bradyarrhythmia) when you start taking ZEPOSIA. ZEPOSIA may cause your heart rate to temporarily slow down, especially during the first 8 days that you take ZEPOSIA." *See* Exhibit B at Medication Guide. The Medication Guide also instructs patients that "[y]ou will receive a 7-day starter pack. You must start ZEPOSIA by slowly increasing doses over the first week. Follow the dose schedule in the table below. This may reduce the risk of slowing of the heart rate." *See* Exhibit B at Medication Guide.

How should I take ZEPOSIA?

You will receive a 7-day starter pack. You must start ZEPOSIA by slowly increasing doses over the first week. Follow the dose schedule in the table below. This may reduce the risk of slowing of the heart rate.

Days 1-4	Take 0.23 mg (capsule in light grey color) 1 time a day
Days 5-7	Take 0.46 mg (capsule in half-light grey and half-orange color) 1 time a day
Days 8 and thereafter	Take 0.92 mg (capsule in orange color) 1 time a day

.

See Exhibit B at Medication Guide.

70. The Medication Guide also lists precautions for how to take ZEPOSIA® including: "[t]ake ZEPOSIA exactly as your healthcare provider tells you to take it"; "[t]ake ZEPOSIA 1 time

each day"; "[s]wallow ZEPOSIA capsules whole"; "[d]o not skip a dose"; "[s]tart taking ZEPOSIA with a 7-day starter pack"; and "[i]f you miss 1 or more days of your ZEPOSIA dose during the first 14 days of treatment, talk to your healthcare provider. You will need to begin with another ZEPOSIA 7-day starter pack." *See* Exhibit B at Medication Guide.

71. Additionally, Defendants' website for ZEPOSIA® for healthcare providers (www.zeposiahcp.com) has a webpage devoted to "Initiation and Dosing" (e.g., www.zeposiahcp.com/ulcerative-colitis/initiation-and-dosing). A true and correct copy of the ZEPOSIA® "Initiation and Dosing" webpage is attached hereto as Exhibit D. The ZEPOSIA® "Initiation and Dosing" webpage describes the "ZEPOSIA 7-day Titration Schedule" and provides an image of the "ZEPOSIA Starter Pack." *See* Exhibit D.

72. The ZEPOSIA® "Initiation and Dosing" webpage (Exhibit D) also provides a link to a "Dosing, Initiation, and Patient Support Guide." A true and correct copy of the ZEPOSIA® "Dosing, Initiation, and Patient Support Guide" is attached hereto as Exhibit E. The ZEPOSIA® "Dosing, Initiation, and Patient Support Guide" instructs healthcare providers on "the steps to get your patients started" including "STEP 1: ASSESSMENTS PRIOR TO FIRST DOSE" and "STEP 2: INITIATE — Initiate ZEPOSIA with a 7-day titration." *See* Exhibit E at 2-7. The ZEPOSIA® "Dosing, Initiation, and Patient Support Guide" also instructs that the "up-titration schedule should be used to reach the maintenance dose to attenuate heart rate reductions, as a transient decrease in heart rate and AV conduction delays may occur." *See* Exhibit E at 7.

7-DAY STARTER PACK Blister Package

73. Moreover, on information and belief, Defendants provide ZEPOSIA® capsules in a "7-DAY STARTER PACK" product blister package, that specifically directs patients and healthcare providers to practice the claimed method for administration.

74. The ZEPOSIA® label states that ZEPOSIA® is supplied in a "7-Day Starter Pack" ("7-

capsule starter pack containing: (4) 0.23 mg ozanimod capsules and (3) 0.46 ozanimod mg capsules") and a "Starter Kit" ("7-Day Starter Pack and 0.92 mg 30-count Bottle"). *See* Exhibit B at 16.1 (How Supplied). Defendants' ZEPOSIA® "Initiating and Dosing" webpage for healthcare providers depicts an image of the "7-DAY STARTER PACK" blister package (reproduced below). *See* Exhibit D. The ZEPOSIA® "Dosing, Initiation, and Patient Support Guide" also depicts the "7-DAY STARTER PACK." *See* Exhibit E at 7. The ZEPOSIA® "Dosing, Initiation, and Patient Support Guide" also lists a "ZEPOSIA Starter Kit," which is "[a] 7-day Starter Pack along with a 30-day supply of ZEPOSIA" under "Initiation Support," a part of "THE ZEPOSIA 360 SUPPORT™ PROGRAM" provided by Defendants. *See* Exhibit E at 8.

75. The ZEPOSIA® capsules "7-DAY STARTER PACK" packaging instructs a method for administering ZEPOSIA® involving an initial treatment phase followed by dose up-titration: "Starting at DAY 1, take one capsule orally each day," where days 1-4 are 0.23 mg once daily (i.e., one quarter of the target dose) and days 5-7 are 0.46 mg once daily (i.e., one half of the target dose):

.

See Exhibit D. Again, the initial treatment phase followed by dose-up titration instructed by the "7-DAY STARTER PACK" (and ZEPOSIA® label) is nearly identical to the method described in the '867 patent: "4 days with 10 mg once daily [i.e., one quarter of the target dose], followed by 4 days with 20 mg once daily [i.e., one half of the target dose], and [thereafter] 40 mg once daily [i.e., the target dose]." '867 patent at 7:8-45 & Table 1.

76. The colored capsules of the "7-DAY STARTER PACK" correspond to the descriptions given in the ZEPOSIA® label and Medication Guide, for example, "Days 1-4" "Take 0.23 mg (capsule in light grey color) 1 time a day," "Days 5-7" "Take 0.46 mg (capsule in half-light grey and half-orange color) 1 time a day," and "Days 8 and thereafter" "Take 0.92 mg (capsule in orange color) 1 time a day." *See* Exhibit B at Medication Guide; *see also* Exhibit B at 3 (Dosage Forms and Strengths), 16.1 (How Supplied).

'867 Patent Dependent Claims 2, 4, 5, and 6

77. The ZEPOSIA® label directs patients to administer and/or use, and healthcare providers to prescribe and/or administer, ZEPOSIA® in a manner that also meets each limitation of at least dependent claims 2, 4, 5, and 6 of the '867 patent.

78. Claim 2 depends from claim 1, and adds the limitation "wherein the initial dose below the target dose is between 2- to 5-fold lower than the target dose." Again, the ZEPOSIA® label, Medication Guide, and "7-DAY STARTER PACK" packaging all instruct a method for administering ZEPOSIA® involving an initial treatment phase followed by dose up-titration, with days 1-4 at 0.23 mg once daily (i.e., one quarter of the target dose), which is 4-fold lower than the target dose of 0.92 mg. *See* Exhibit B at 2.2 (Recommended Dosage for Multiple Sclerosis and Ulcerative Colitis), Medication Guide; Exhibit D. Thus, the initial dose below the target dose is between 2- to 5-fold lower than the target dose, namely, 4-fold lower than the target dose.

79. Claim 4 also depends from claim 1, and adds the limitation "wherein the dose below

the target dose is administered to the subject during the initial 2 to 4 days of the treatment." Again, the ZEPOSIA® label, Medication Guide, and "7-DAY STARTER PACK" packaging all instruct a method for administering ZEPOSIA® involving an initial treatment phase followed by dose up-titration, with days 1-4 at 0.23 mg once daily (i.e., one quarter of the target dose). *See* Exhibit B at 2.2 (Recommended Dosage for Multiple Sclerosis and Ulcerative Colitis), Medication Guide; Exhibit D. Thus, the dose below the target dose is administered to the subject "during the initial 2 to 4 days of the treatment," namely, during the initial 4 days of treatment.

80. Claim 5 similarly depends from claim 1, and adds the limitation "wherein the dose below the target dose is administered at a dosing frequency of once or twice daily." Claim 6 depends from claim 2 and adds the same limitation. Again, the ZEPOSIA® label, Medication Guide, and "7-DAY STARTER PACK" packaging all instruct a method for administering ZEPOSIA® involving an initial treatment phase followed by dose up-titration, with days 1-4 at 0.23 mg once daily (i.e., one quarter of the target dose), with the doses taken "once daily." *See* Exhibit B at 2.2 (Recommended Dosage for Multiple Sclerosis and Ulcerative Colitis), Medication Guide; Exhibit D. Thus, the dose below the target dose is administered at a dosing frequency of "once or twice daily," namely, once daily.

Infringement Under 35 U.S.C. §§ 271(b) and (c)

81. Defendants have actively induced infringement by others, or contributed to infringement by others, of at least claims 1, 2, 4, 5, and 6 of the '867 patent under 35 U.S.C. §§ 271(b) and (c), either literally or under the doctrine of equivalents.

82. On information and belief, Defendants had and have an affirmative intent to actively induce or contribute to infringement by others of one or more claims of the '867 patent, either literally or under the doctrine of equivalents.

83. On information and belief, Defendants are aware, have knowledge, and/or are willfully

blind to the fact that patients administer and/or use, and healthcare providers prescribe and/or administer, ZEPOSIA® in a manner that directly infringes at least claims 1, 2, 4, 5, and 6 of the '867 patent, either literally or under the doctrine of equivalents. Moreover, on information and belief, Defendants are aware, have knowledge, and/or are willfully blind to the fact that their affirmative acts constitute indirect infringement.

84. On information and belief, Defendants have knowingly or with willful blindness induced or contributed to another's direct infringement of at least claims 1, 2, 4, 5, and 6 of the '867 patent, either literally or under the doctrine of equivalents, by at least Defendants' package insert for ZEPOSIA®.

85. Defendants have knowledge of and are aware of the '867 patent, including due to the filing of this Complaint, as well as for other reasons such as those recited in paragraphs 49-54 of this Complaint. On information and belief, Defendants' knowledge of the '867 patent together with their knowledge of their own product, ZEPOSIA®, gave Defendants knowledge that patients' and healthcare providers' use of ZEPOSIA® according to its label constitutes patent infringement.

86. On information and belief, Defendants' inducing acts include marketing ZEPOSIA®, and supporting the ongoing use of ZEPOSIA® by providing patients and healthcare providers with instructions for its use, including the ZEPOSIA® label, Medication Guide, "7-DAY STARTER PACK" packaging, ZEPOSIA® "Initiation and Dosing" webpage for healthcare providers, and ZEPOSIA® "Dosing, Initiation, and Patient Support Guide." *See* Exhibit B at, *e.g.*, 2.2 (Dosing Information), Medication Guide; Exhibit D; Exhibit E. In addition to instructing healthcare providers to initiate treatment with the "ZEPOSIA 7-day titration schedule" and to use the "7-DAY STATER PACK" and "ZEPOSIA Starter Kit," the ZEPOSIA® "Dosing, Initiation, and Patient Support Guide" also states that "[w]e are here to help along the way with our ZEPOSIA 360 Support™ Program" and that "If you have any questions about getting a patient started on ZEPOSIA, please give us a call!" followed by the

phone number and email address for "Bristol Myers Squibb Medical Information." *See* Exhibit E at 15.

87. On information and belief, Defendants are aware that ZEPOSIA® is especially made and adapted for use in infringement of the '867 patent. Defendants' instructions for the initiation of administration of ZEPOSIA®, by a method that infringes the '867 patent, are required for patient safety. Defendants' customers necessarily infringe the '867 patent when they use ZEPOSIA® in accordance with Defendants' instructions and for its indicated use. ZEPOSIA® is not a staple article or commodity of commerce, and ZEPOSIA® does not have a substantial non-infringing use when used as instructed. On information and belief, Defendants have no practical ability to modify or use ZEPOSIA® for its indicated uses so as to avoid infringement of the '867 patent.

88. Defendants are not licensed under the '867 patent.

89. Actelion has been damaged and will continue to be damaged by Defendants' infringement of the '867 patent. For example, Actelion has suffered damages at least in the form of lost sales of at least PONVORY® as a result of Defendants' infringement of the '867 patent.

90. Actelion has suffered and will continue to suffer irreparable harm unless and until Defendants' infringing activities are enjoined by this Court. Actelion does not have an adequate remedy at law.

91. Despite Defendants' knowledge of the '867 patent and their infringing activities thereof, Defendants have continued to manufacture, use, offer to sell, sell, and/or import ZEPOSIA®. Defendants' infringement of the '867 patent has been willful, making this an exceptional case. Accordingly, Actelion is entitled to an award of increased damages, attorneys' fees, and costs.

PRAYER FOR RELIEF

WHEREFORE, Actelion respectfully requests a judgment that:

A. Defendants have infringed and, unless enjoined, will continue to infringe the '867

patent;

B. Enjoins Defendants and their officers, agents, servants, and employees from further infringement of the ’867 patent;

C. Awards Actelion damages adequate to compensate for Defendants’ infringement of the ’867 patent under 35 U.S.C. § 284, including lost profits and/or a reasonable royalty;

D. Declares that this is an exceptional case under 35 U.S.C. § 285;

E. Awards increased damages, attorneys’ fees, and costs for Defendants’ willful infringement;

F. Awards pre-judgment and post-judgment interest, including costs;

G. Awards any other further relief as this Court deems just and proper.

JURY DEMAND

Actelion hereby demands trial by jury on all issues so triable.

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October 15, 2021

LOCAL CIVIL RULE 11.2 CERTIFICATION

Pursuant to Local Civil Rule 11.2, the undersigned, attorney of record for Plaintiffs, hereby certifies that to the best of my knowledge and based upon the information available to me, the matter in controversy is not the subject of any other action pending in any court or of any pending arbitration or administrative proceeding.

Dated: October 15, 2021

s/ *Keith J. Miller, Esq.*
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